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Please find below and/or attached an Office communication concerning this application or proceeding.

•	Application N	Applicant(s)			
Office Action Commons	09/462,416	REVEL ET AL.			
Office Action Summary	Examiner	Art Unit			
	Daniel Kolker	1646			
The MAILING DATE of this communication appears on the cover sheet with the correspondence address Period for Reply					
A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION. - Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication. - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely. - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).					
Status					
1)⊠ Responsive to communication(s) filed on <u>03 Mar</u> 2a)□ This action is FINAL . 2b)⊠ This 3)□ Since this application is in condition for allowant closed in accordance with the practice under E	action is non-final. ace except for formal matters, pro				
Disposition of Claims					
4)	vn from consideration.	ment.			
Application Papers					
9) The specification is objected to by the Examiner 10) The drawing(s) filed on is/are: a) access applicant may not request that any objection to the Replacement drawing sheet(s) including the correction of the option of of the op	epted or b) objected to by the Eddrawing(s) be held in abeyance. See ion is required if the drawing(s) is obj	e 37 CFR 1.85(a). lected to. See 37 CFR 1.121(d).			
Priority under 35 U.S.C. § 119					
 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) All b) Some * c) None of: 1. Certified copies of the priority documents have been received. 2. Certified copies of the priority documents have been received in Application No 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). * See the attached detailed Office action for a list of the certified copies not received. 					
Attachment(s) 1) Notice of References Cited (PTO-892) 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 20 April 2000.	4) Interview Summary Paper No(s)/Mail Da 5) Notice of Informal P 6) Other:				

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DETAILED ACTION

The remarks and amendment of 3 March 2002 have been entered. Applicant has withdrawn claims 16 - 26 and 37, and has added new claims 39 - 44. Claims 2 - 7, 9 - 11, 33, and 38 - 44 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All rejections not reiterated are withdrawn.

Election/Restrictions

Applicant has reiterated the traversal of the restriction requirement. However, this requirement had been made final in the first Office action on the merits (paper 13, dated 15 January 2002). Should applicant desire reconsideration of the restriction requirement, the proper avenue is via petition, and cannot be reconsidered by the examiner at this time (see MPEP § 818.03(c) and 37 CFR § 1.144). It is acknowledged that should any product claim currently being examined be found allowable, Applicant retains the right to have process claims examined that depend from allowed subject matter.

Information Disclosure Statement

The information disclosure statement filed 4 December 2001 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. There is no list of references attached to the letter filed 4 December 2001.

Note that the Information Disclosure Statement filed 20 April 2000 has been considered; form 1449 is attached. The references by Mackiewicz et al. and Kollet et al. are not in proper format for publication on the face of a patent as they exclude the name and volume number of the publication. However the references have been considered.

Claim Objections

Applicant is advised that should claim 42 be found allowable, claim 43 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application

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are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

REJECTIONS WITHDRAWN

Claim Rejections - 35 USC § 112

In the office action dated 2 October 2002, claims 2, 4 – 7, 9 – 11, 33, and 38 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, particularly because it was not clear which sequences applicant was attempting to claim by use of the terms "Ig-like domain" and "receptor pre-membrane domain", and "naturally occurring", as well as because the naturally occurring glycosylation pattern was not disclosed. Ig-like domain appears to be an art-accepted term (see, for example, Yawata et al. EMBO J 12(4):1705-1712). The brief description of Figure 3 clearly indicates the receptor pre-membrane region in relation to the well-defined cytokine C-domain and art accepted transmembrane domain. Applicant indicates, on p. 8 of the remarks filed 3 March 2002, that "the naturally occurring sequence of sIL-6R and IL-6 are known and are part of SEQ ID NO:7". Applicant has argued that the specific glycosylation pattern is not what is being claimed, and does not necessarily have the natural glycosylation pattern. These arguments are convincing; the rejection of claim 38 under 35 U.S.C. 112, second paragraph is withdrawn. Claims 2, 4-7, 9-11, and 33 had been rejected for depending on an indefinite base (or intermediate) claim. The rejections of these claims under 35 U.S.C. 112, second paragraph are also withdrawn.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 112

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the office action dated 2 October 2002, the claim was considered indefinite because it was not possible to determine the metes and bounds of the claim when it contained the language "very short, non-immunogenic linker of about 3 amino acid residues". Applicant has amended the claim to delete the term "very short". However, the claim still includes the term "about 3 amino acids". Deletion of the term "very short" does not give a precise definition

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of the term "about 3". It is unclear whether 0, 1, 2, 4, 10, or 40 might qualify as "about 3". Therefore, the rejection of claim 3 under 35 USC 112, second paragraph remains.

REJECTIONS NECESSITATED BY AMENDMENT

Claim Rejections - 35 USC § 112

Claim 44 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polypeptides with amino acid sequences SEQ ID NO:7 and SEQ ID NO:7 wherein the tripeptide linker at residues 357-359 is replaced by SEQ ID NO:1, does not reasonably provide enablement for the full range of analogs encoded by nucleic acids which hybridize under the recited conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claim is drawn to molecules which are analogs of chimeric sIL-6R/IL-6 polypeptides, encoded by nucleic acids which hybridize to certain DNA sequences under stringent conditions, as defined in the claim. Hybridization and the factors that influence its specificity, are described in length in the teachings of Sambrook et al. (Molecular Cloning – A Laboratory Manual, pp. 9.47 – 9.51 and 11.48 – 11.49). Given the degeneracy of the genetic code, hybridization under the conditions recited in the claim would be expected to identify a vast array of molecules, many of which would differ by more than thirty amino acids, would have immunogenic linkers, or would otherwise be beyond the scope of the two polypeptide sequences disclosed in the specification. Because the specification does not provide guidance as to where in the nucleic acid sequence any changes could be made without affecting function of the chimeric polypeptide, and since the claim does not recite any structural limitations, it is not possible to make the invention in scope commensurate with the claims. Therefore claim 44 is rejected for failing the enablement requirement of 35 U.S.C. 112, first paragraph.

Claim 44 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 44 is drawn to polypeptides encoded by polynucleotides that hybridize to certain nucleic acid sequences, under stringent conditions. The claim recites stringent conditions as those conditions that "include" washing conditions 12 – 20 °C below the calculated melting

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temperature. However, this is not a structural limitation, and furthermore is written so broadly as to include multiple hybridization, washing, and re-hybridization steps, thereby rendering the current limitation meaningless. This rejection could be overcome by recitation of specific hybridization conditions, including the composition of the hybridization buffer, the temperature and duration of the hybridization, the number of washes to be performed, and the temperature, salt concentration, detergent concentration, and duration of each washing step, provided that adequate written description is present in the specification as originally filed. A skilled artisan would not be able to determine which sequences are being claimed, at either the amino acid or nucleic acid level, by the stringent conditions listed in claim 44.

Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim encompasses a polypeptide encoded by a nucleic acid molecule which hybridizes under "stringent conditions." Though the claim recites a range of hybridization temperatures, this is merely exemplary, as hybridization can include many other as yet undescribed steps. Stringent conditions are defined in a similar indefinite fashion on page 25 of the specification. The term "stringent conditions" is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 44 is rejected under 35 U.S.C. 102(a) as being anticipated by Fischer et al. (Nature Biotechnology 15:142 – 145). Part (b) of the claim is drawn to polypeptides encoded by sequences which hybridize to certain DNA sequences under stringent conditions. The claim defines stringent conditions as including, but not limited to, washing 12 - 20 °C below the calculated T_m of the hybrid under study. Fischer et al. teach a fusion protein that differs from that of SEQ ID NO:7 only in the linker region and in the short non-functional regions of sIL-6R. In fact, the chimeric fusion protein disclosed by Fischer is identical to that of SEQ ID NO:7 from residues 113 - 323 of human soluble IL-6R and from residues 29 - 212 of IL-6 (see

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specification, p. 17, second paragraph and Fischer, p. 145, Experimental Protocol). Fischer et al. also disclose that their fusion protein is capable of triggering dimerization of gp130. These protein sequences were separately reverse-translated to DNA sequences by the program available at http://arbl.cvmbs.colostate.edu/molkit/rtranslate/. The Tm of a hybrid can be calculated using the software available at

http://www.basic.northwestern.edu/biotools/OligoCalc.html. The first region (residues 113 – 323 of sIL-6R) is encoded by a nucleic acid 633 bases long, 38% GC. Tm for this region is predicted to be 93 °C, using the salt-adjusted value and 50 nM sodium. The second region (residues 29 – 212 of IL-6) is encoded by a nucleic acid that is 576 bases long, 33% GC, and Tm of 91 °C. Together these regions are 1182 bases, separated by a linker region 13 amino acids (i.e. 39 nucleotides) long; the predicted Tm is 93 °C. The sequence claimed by applicant (i.e. the same sequence as above, with residues 20 – 112 and 324 – 356 of sIL-6R added on) has a Tm of 94 °C. Because the sequences have Tm predicted within 1 degree of each other, the nucleic acid encoding the molecule disclosed by Fischer et al. would inherently hybridize to a nucleic acid sequence encoding the fusion protein of claim 38 under conditions which include washing conditions 12 - 20 °C below the calculated T_m of the hybrid. Even though the sequence disclosed by Fischer et al. does not meet all the elements of part (a) of claim 44, part (b) does not require all the elements of (a), rather it only requires that the analog hybridize under the recited conditions and be capable of triggering dimerization of gp130.

NEW REJECTIONS

Claim Rejections - 35 USC § 112

Claims 2-5, 9-11, 33, and 38-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for two chimeric sIL-6R/IL-6 fusion proteins that vary only in the linker region, does not reasonably provide enablement for chimeric fusion proteins with no linker, wherein the linker is not a short polypeptide, or wherein substitutions, additions, or deletions in either the sIL-6R or IL-6 moieties of the chimeric fusion protein have been made. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims are drawn to specific chimeras and analogs. In the previous office action, the examiner had considered the claims enabled for the specific chimeras. Claim 38 has been amended to include, in part (a), functional language that

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necessitates that the linker in the chimera, if present, must not prevent triggering dimerization of gp130 in human cells. Such language also exists in part (b) of claim 38. These changes do help to clarify the scope of the claim, but it is still drawn to non-enabled subject matter, including analogs in which anywhere between zero and 30 amino acid residues are added, deleted, or substituted anywhere in the polypeptide. As noted on p. 4 of the previous office action, the specification, while being enabling for two SEQ ID NO:7 and SEQ ID NO:7 in which the 13-residue linker of SEQ ID NO:1 is substituted for the tri-peptide at residues 357-359, does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. In the previous office action, the examiner had considered the specification enabling for the analogs in which up to 30 insertions deletions, or substitutions had been made in the reference sequence. Upon further consideration, the examiner has determined that the specification is not enabling for any analogs; enablement is limited to the two chimeric molecules whose structures are recited in claims 6 and 7, for the reasons enumerated below.

The scope of claim 38 includes chimeric fusion proteins both with and without a linker molecule. The specification contemplates, at page 17, lines 24 – 26, the production of chimeric fusion proteins without linkers, but the disclosure is limited to two molecules that have linkers. The claim requires that the linker, if present, not prevent dimerization of gp130. However, the claim is sufficiently broad to include chimeric proteins without linkers that fail to dimerize gp130. The limitation in the claim is functional, not structural, and applies only to the linker, not the entire peptide. Applicant has not shown which regions of either protein moiety or the linker region are necessary for dimerization of gp130, and has not demonstrated whether chimeric fusion proteins without linkers will dimerize gp130. The post-filing date teachings of Tepper et al. (U.S. Patent 6,372,207) indicate that the preferable embodiment of fusion proteins between cytokines and their receptors is one in which the linkers are peptide sequences up to about 30 amino acids (see particularly column 7, lines 39 - 40). Fischer et al. teach that the distance between IL-6 and sIL-6R is about 40 Å (see p. 143, first line), and that this distance can be spanned by 33 - 36 residue peptides, or by shorter sequences, including a 13-residue sequence. Therefore it is not reasonable to expect that chimeric fusion proteins without linkers can be used in the same manner as the two disclosed sequences. Applicant has not demonstrated that chimeric fusion proteins lacking a linker will dimerize gp130, and since the art

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teaches that preferred embodiments of chimeric proteins between cytokines and their receptors include linkers, the claim is not enabled in its full scope.

Claim 38, part (b), is drawn to analogs that differ by up to 30 amino acids anywhere in the sequence of either sIL-6R, IL-6, or the linker molecule. The only functional limitation is that the changes not prevent the chimeric molecule from triggering gp130 dimerization. The claim is not limited to insertions in the linker region; it includes insertions, deletions, and substitutions, in any combination, in any part of the linker, sIL-6R, or IL-6 sequence. The prior art teaching of Paonessa et al. (EMBO J 14(9):1942-1951) indicates that changing just two sites on IL-6 interferes with its ability to interact with and dimerize gp130. This indicates that it would be difficult to predict whether any given change in the sequence would result in an inoperative protein; the level of predictability in the art is low. From looking at a sequence listing alone, a skilled artisan would not be able to determine how to make the full range of molecules that applicant has claimed as analogs in part (b) of claim 38 without resorting to undue experimentation. The claim does not include structural limitations, i.e. it does not tell which regions of the protein must be conserved in order for it to have the specified activity. The claim is akin to a single means claim, i.e., where a means recitation does not appear in combination with another recited element of means and is subject to an undue breadth rejection under 35 USC 112, first paragraph because the specification at most would only disclose those means known to the inventor at the time of the invention, see in particular MPEP 2164.08(a).

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988). The specification provides only two examples of fusion proteins, which differ only in the linker region. There is no guidance as to which regions of either IL-6 or sIL-6R can be altered without changing the ability of the fusion protein to trigger dimerization of gp130. Thus, the specification fails to teach the skilled artisan how to make and use the claimed polypeptides without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the invention for the above stated purposes.

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Because there is no guidance in the specification as to which structural elements must be conserved in order to ensure that the protein is functional, the lack of predictability in the art, the limitation of examples to just two sequences that differ only in the linker region, and the complex nature of the invention, undue experimentation would be required of the skilled artisan to make and use the claimed invention. Therefore claim 38 remains rejected. Claims 2 - 5, 9 - 11, 33, and 39 - 44 are rejected because they depend from a rejected base or intermediate claim.

Claims 2 – 5, 9 – 11, 33, and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 38 is drawn to a chimeric soluble IL-6R/IL-6 protein, consisting of "the naturally occurring sequence of sIL-6R" fused to "the naturally occurring sequence of IL-6" with up to 30 insertions, deletions, or substitutions anywhere along the sequence. The specification discloses two sequences (depicted in figures 3 and 11), which both contain sIL-6R and IL6, joined by a variable linker region. The claim as written is sufficiently broad to include anywhere from zero to thirty insertions, deletions, or substitutions at any point along the entire fusion protein, as well as undescribed allelic variants from any species which contains genes encoding IL-6 and IL-6R.

The claims are akin to example 6 of the Revised Interim Written Description Guidelines Training Materials, available on the USPTO's web site at http://www.uspto.gov/web/offices/pac/writtendesc.pdf, directed to the recitation of genes. The claims are drawn to genera of nucleic acid sequences, including those with regulatory elements, untranslated regions, allelic variants, mutation sequences, and sequences across species as encompassed by the terms "naturally occurring sequence". The art teaches that the interactions of untranslated regions of genes is complex and gene-specific (see Mazumder et al., 2003. Trends in Biochemical Sciences 28:91-98, particularly the paragraph that spans pp. 91 – 92). Applicant has not indicated which regions of either sIL-6R or IL-6 are essential for dimerization of gp130, and the teachings of Paonessa et al. indicate that it would be difficult to predict which regions of the protein must be retained so that dimerization of gp130 will occur. One of skill in the art would not be able to know, based on the disclosure, which elements of IL-6 and sIL-6R are necessary for dimerization, and which could be altered or deleted, or where insertions could

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be made. Therefore claims 2 - 5, 9 - 11, 33, and 38 fail to meet the written description requirement and stand rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 9 - 11, 33, 38 - 41, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fischer et al., in view of Lust et al. (Curr Top Microbiol Immunol, 194:199-206). Claim 38, part a, is drawn to a chimeric sIL-6R/IL-6 fusion protein, transcribed from a single nucleic acid sequence, which includes the lg domain and receptor pre-membrane domains of sIL-6R. Fischer et al. teach a chimeric fusion protein comprised of a shortened version of sIL-6R, a peptide linker, and IL-6. Fischer et al. do not teach the use of the complete, naturally occurring sIL-6R, although they do contemplate its use. See specifically p. 142, third paragraph, which states "[w]e demonstrate that covalently linking human IL-6 to the human sIL-6R results in a highly biologically active fusion protein", and the fourth paragraph, which describes the construction of the fusion protein. The fusion peptide made by Fischer et al. includes a truncated form of sIL-6R. However, Fischer et al. do not indicate that this truncation confers any advantage, or even difference, over naturally occurring sIL-6R. In fact, Fischer et al. teach that the N-terminal region of sIL-6R, including the Ig domain, and the C-terminal tether domain (i.e. receptor pre-membrane domain) do not contribute to the protein's biological activity (p. 143, end of paragraph that begins on p. 142). Furthermore, circular dichroism spectroscopy shows that the fusion protein folds as one would predict a product composed of isolated IL-6 and IL-6R would (p. 143, first complete paragraph). Lust et al. teach the sequence of the soluble form of the IL-6R (sIL-6R). It would have been obvious to one of ordinary skill in the art to use the naturally occurring sequence of sIL-6R in the fusion protein instead of the shortened one used by Applicant, with a reasonable expectation of success, given that the sequences omitted by Applicant's work do not confer any changes in biological activity. A motivation for doing so would be to obviate the need to construct a new plasmid containing the shortened version of the sIL-6R gene. Since sIL-6R had already been sequenced, using the full-length

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sequence would have actually resulted in less work than using the truncated version. Furthermore, Fischer et al. contemplated the use of full-length human IL-6 and sIL-6R (see p. 142, first column, third paragraph). Therefore, claims 2, 9 – 11, and 38 – 41 are rejected. Claim 3 depends from the same interpretation of claim 38, and therefore is also rejected. Note that claims 9 – 11 are product-by-process claims; they stand rejected because the claimed product is deemed obvious under 35 U.S.C. § 103; see MPEP 2113. A product made by any other process renders a product-by-process claim unpatentable. See In re Marosi, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983) and In re Thorpe, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985).

Claim 33 is drawn to a pharmaceutical composition with the polypeptide of claim 38 as an active ingredient, and a pharmaceutically acceptable carrier. Claim 38 has been rejected under 35 U.S.C. 103. Because Fischer et al. treated cells with a pharmaceutical composition comprising their fusion protein (see Figures 4 – 6, for example), the teachings of Fischer meet the limitation of claim 33 as well.

Conclusion

It is believed that all pertinent remarks and arguments have been addressed. Claims 2 - 5, 9 - 11, 33, and 38 - 44 are rejected. Claims 6 and 7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.

February 16, 2005

SHARON L TURNER, PH.D.

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